Secretomes of human pluripotent stem cell-derived smooth muscle cell progenitors upregulate extracellular matrix metabolism in the lower urinary tract and vagina.

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Public Summary:
Adult mesenchymal stem cells (MSCs) have been studied extensively for regenerative medicine; however, the cells do not expand well in the laboratory, and the long culture time induces cell senescence. MSCs also contribute to tissue repair through secretion of proteins that promote regeneration of surrounding cells in the treated tissue. In this study, we sought to examine the secreted proteins of human smooth muscle cell progenitors (pSMC) on the urethra and adjacent vagina of stress urinary incontinence rodents. We use human pluripotent stem cell (PSC) lines to derive pSMCs to overcome the issue of decreased cell growth in tissue culture and to obtain a homogenous cell population. Our studies revealed that the proteins secreted by pSMCs improved urethral function in the stress urinary incontinent rodents compared to those treated with only saline. The protein treatment also increased collagen and elastin content in the damaged rat urethra.

Scientific Abstract:
BACKGROUND: Adult mesenchymal stem cells (MSCs) have been studied extensively for regenerative medicine; however, they have limited proliferation in vitro, and the long culture time induces cell senescence. MSCs also contribute to tissue repair through their paracrine function. In this study, we sought to examine the paracrine effects of human smooth muscle cell progenitors (pSMC) on the urethra and adjacent vagina of stress urinary incontinence rodents. We use human pluripotent stem cell (PSC) lines to derive pSMCs to overcome the issue of decreased proliferation in tissue culture and to obtain a homogenous cell population. METHOD: Three human PSC lines were differentiated into pSMCs. The conditioned medium (CM) from pSMC culture, which contain pSMC secretomes, was harvested. To examine the effect of the CM on the extracellular matrix of the lower urinary tract, human bladder smooth muscle cells (bSMCs) and vaginal fibroblasts were treated with pSMC-CM in vitro. Stress urinary incontinence (SUI) was induced in rats by surgical injury of the urethra and adjacent vagina. SUI rats were treated with pSMC-CM and monitored for 5 weeks. Urethral pressure testing was performed prior to euthanasia, and tissues were harvested for PCR, Western blot, and histological staining. Kruskal-Wallis one-way ANOVA test and Student t test were used for statistical comparisons. RESULTS: pSMC-CM upregulated MMP-2, TIMP-2, collagen, and elastin gene expression, and MMP-9 activity in the human bladder and vaginal cells consistent with elastin metabolism modulation. pSMC-CM treatment in the SUI rat improved urethral pressure (increase in leak point pressure compared to intact controls, $p < 0.05$) and increased collagen and elastin expression in the urethra and the adjacent vagina. CONCLUSION: Conditioned media from smooth muscle cell progenitors derived from human pluripotent stem cells improved urethral leak point pressure and collagen and elastin content in the SUI rat. These findings suggest a novel therapeutic potential for PSC-based treatments for SUI and pelvic floor disorders where tissues are affected by collagen, elastin, and smooth muscle loss.